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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,627	01/09/2002	Xiao-Tao Chen	PH-7211	6514
23914	7590	01/22/2004	EXAMINER	
STEPHEN B. DAVIS BRISTOL-MYERS SQUIBB COMPANY PATENT DEPARTMENT P O BOX 4000 PRINCETON, NJ 08543-4000			LIU, HONG	
			ART UNIT	PAPER NUMBER
			1624	
DATE MAILED: 01/22/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

## Application No.

10/043,627

## Applicant(s)

CHEN ET AL.

## Examiner

Hong Liu

## Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE \_\_\_\_\_ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on 14 November 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4 and 6-26 is/are rejected.
- 7) ☒ Claim(s) 5 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

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### **DETAILED ACTION**

Claims 1-26 are pending in this application.

This action is in response to the applicants' amendment and reply filed on November 14, 2003.

### **Response to Arguments**

Applicants' arguments and amendments filed on November 14, 2003 have been fully considered. However, applicants' amendments have not overcome the rejection and the rejoined method claims are rejected under 35 U.S.C. § 112, first paragraph, for the reasons given below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Election/Restrictions***

The amended claims are object to as they still contain the non-elected subject matter which was withdrawn from consideration in the previous office action. Applicants are reminded that compounds of group I of the restriction requirement are compounds of formula I wherein Z<sup>a</sup> is quinoline, U<sup>a</sup> is oxygen, Z is phenyl, Ring B is a five or six membered, monocyclic, saturated heterocyclic ring. Because applicants elected Group I, the structure search was carried out based on the elected compounds. If the scope of the amended claims is still broader than that of the elected group, the patentability of the compounds cannot be determined because the search did not extend beyond the scope of the elected compounds.

***Claim Rejections - 35 USC § 112***

Rejection of claims under 35 U.S.C., 112, first paragraph, is maintained for reasons already made of record in the previous office action. Applicants have narrowed the scope of the claims considerably. However, Z<sup>a</sup> is still not limited to quinoline and U<sup>a</sup> is not limited to oxygen. As stated in the previous office action, the synthesis scheme shows that the compounds can be prepared by reacting intermediate 2 or a spirolactone 6 with HS-Z-U<sup>a</sup>-X<sup>a</sup>-Y<sup>a</sup>-Z<sup>a</sup> to obtain the final products (pages 40 and 41). There is no teaching in the following examples how the starting materials of HS-Z-U<sup>a</sup>-X<sup>a</sup>-Y<sup>a</sup>-Z<sup>a</sup> can be obtained wherein U<sup>a</sup> is absent or other than an oxygen and R<sup>1a</sup> and R<sup>1b</sup>, R<sup>a</sup> and R<sup>a1</sup>, two R<sup>3</sup> form rings. For this reason, the amended scope of the claims is still not enabled.

Claims 7-10 and 15-26 are drawn to a method of treating MMP or TNF-alpha-mediated disease. These claims are interpreted to include any and all disorders associated with this particular mode of action. The specification reads on any and all stroke, arthritis, cancer, AIDS, sepsis, scleritis in which cells receive pro-inflammatory signals. However, there is no teaching in the specification that the instant compounds could inhibit TNF alpha production, let alone treatment of TNF alpha associated diseases. On page 110 of the specification, there is only one *in vitro* assay of the inhibitory activity of aggrecanase. Aggrecanase is only one of the proteinases in the MMP family. Even though applicants are able to show that all the compounds within the genus are effective in inhibiting aggrecanase, one ordinary skill in the art would not reasonably come to the conclusion that the compounds are effective in treating diseases associated with other metalloproteinases in the MMP family. Applicants provide no compelling evidence that instantly disclosed test is reasonably predictive for one use much less for the disorders listed in

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the claims. Applicants have not demonstrated a nexus between the activity of the compounds and the myriad of divergent utilities in claims 7-10 and 15-26.

Search of the recently published literature reveals that the best matrix metalloproteinase inhibitor in the clinical trial stage has yielded unpredictable results. Steward (Cancer Chemother. Pharmacol., 1999), for instance, point outs that Marimastat, the first matrix metalloproteinase inhibitor that has entered clinical trial, only has some effects on gastric cancer. The phase II study of the drug, particularly in gastric cancer "suggest that matrimastat may have biological activity which reduces tumor growth, but firm evidence of an effect on clinical outcome is still not available." page 59. Therefore, contrary to what applicants urge is enabled, there is no art-recognized evidence of clinical efficacy for the scope being claimed. Competent evidence of art-recognized efficacy for claimed uses needs to be provided. Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the likelihood of in vivo use for all uses being claimed. See *Ex parte Powers*, 220 USPQ 925.

### ***Conclusion***

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action. Any inquiry concerning this communication should be directed to Examiner Hong Liu whose telephone number is (703) 306-5814. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached at (703) 308-4716. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 358-1235.

  
Mukund L. Raymond  
Acting SPE  
**Mukund Shah**  
Art Unit 1624  
**Supervisory Patent Examiner**  
**Art Unit 1624**

hl  
January 14, 2004